

AMENDMENTS TO THE CLAIMS

1. **(Withdrawn)** A method of modulating a biological response in a cell, the method comprising contacting the cell with at least one agent that modulates the expression or activity of Err α or Gabp, wherein the biological response is

- (a) expression of at least one OXPHOS gene;
- (b) mitochondrial biogenesis;
- (c) expression of Nuclear Respiratory Factor 1 (NRF-1);
- (d) β -oxidation of fatty acids;
- (e) total mitochondrial respiration;
- (f) uncoupled respiration;
- (g) mitochondrial DNA replication;
- (h) expression of mitochondrial enzymes; or
- (i) skeletal muscle fiber-type switching.

2-16. **(Canceled)**

17. **(Withdrawn)** A method of determining whether an agent is a potential agent for the treatment of a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function, the method comprising determining whether the agent increases:

- (i) the expression or activity of Err α or Gabp in a cell; or
- (ii) the formation of a complex between a PGC-1 polypeptide and (i) an Err α polypeptide; or (ii) a Gabp polypeptide;

wherein an agent that increases (i) or (ii) is a potential target for the treatment of the disorder.

18-41. **(Canceled)**

42. **(Withdrawn)** A method of identifying a susceptibility locus for a disorder that is characterized by reduced mitochondrial function, glucose intolerance, or insulin intolerance in a subject, the method comprising

(i) identifying at least one polymorphism in a gene, or linked to a gene, wherein the gene (a) has an $Err\alpha$ binding site, a $Gabpa$ binding site, or both; or (b) is $Err\alpha$, $Gabpa$, or $Gabpb$;

(ii) determining whether at least one polymorphism is associated with the incidence of the disorder,

wherein if a polymorphism is associated with the incidence of the disorder then the gene having the polymorphism, or the gene to which the polymorphism is linked, is a susceptibility locus.

43-46. (Canceled)

47. (Withdrawn) A method of determining whether a subject is at risk of developing a disorder which is characterized by reduced mitochondrial function, the method comprising determining whether a gene from the subject contains a mutation which reduces the function of the gene, wherein the gene has an $Err\alpha$ binding site, a $Gapba$ binding site, or both, wherein if a gene from the subject contains the mutation then the subject is at risk of developing the disorder.

48-77. (Canceled)

78. (Withdrawn) A method of detecting statistically-significant differences in the expression level of at least one biomarker belonging to a biomarker set, between the members of a first and of a second experimental group, comprising:

- (a) obtaining a biomarker sample from members of the first and the second experimental groups;
- (b) determining, for each biomarker sample, the expression levels of at least one biomarker belonging to the biomarker set and of at least one biomarker not belonging to the set;
- (c) generating a rank order of each biomarker according to a difference metric of its expression level in the first experimental group compared to the second experimental group;

- (d) calculating an experimental enrichment score for the biomarker set by applying a non-parametric statistic; and
- (e) comparing the experimental enrichment score with a distribution of randomized enrichment scores to calculate the fraction of randomized enrichment scores greater than the experimental enrichment score, wherein a low fraction indicates a statistically-significant difference in the expression level of the biomarker set between the members of the first and of the second experimental group.

79-92. **(Canceled)**

93. **(Previously Presented)** A method of identifying an agent that regulates expression of OXPHOS-CR genes, the method comprising

- (a) contacting (i) an agent to be assessed for its ability to regulate expression of OXPHOS-CR genes with (ii) a test cell; and
- (b) determining whether the expression of at least two OXPHOS-CR gene products show a coordinate increase in the test cell compared to an appropriate control, wherein a coordinate increase in the expression of the OXPHOS-CR gene products indicates that the agent regulates the expression of OXPHOS-CR genes.

94-105. **(Canceled)**

106. **(Previously Presented)** The method of claim 93, wherein a coordinate increase in the expression of the OXPHOS-CR gene products further indicates that the agent is a potential enhancer of the expression or activity of Erra or Gabp.

107. **(Previously Presented)** The method of claim 106, wherein a coordinate increase in the expression of the OXPHOS-CR gene products further indicates that the agent is a potential agent for enhancing mitochondrial biogenesis, expression of Nuclear Respiratory Factor 1 (NRF-1), β -oxidation of fatty acids, total mitochondrial respiration, uncoupled respiration, mitochondrial DNA replication, expression of mitochondrial enzymes, or skeletal muscle fiber-type switching.

108. **(Previously Presented)** The method of claim 93, wherein the agent to be assessed is a small molecule.

109. **(Previously Presented)** The method of claim 93, wherein a coordinate increase in the expression of the OXPHOS-CR gene products indicates that the agent is a potential agent for the treatment of a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function.

110. **(Previously Presented)** The method of claim 93, wherein a coordinate increase in the expression of the OXPHOS-CR gene products further indicates that the agent is a potential agent for increasing expression or activity of *Erra* or *Gabp*.

111. **(Previously Presented)** The method of claim 110, wherein an agent that increases expression or activity of *Erra* or *Gabp* is a potential agent for the treatment of a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function.

112. **(Previously Presented)** The method of claim 110, wherein the test cell is a mammalian cell.

113. **(Withdrawn)** The method of claim 93, further comprising assessing the effect of the agent on mitochondrial number or on a mitochondrial function.

114. **(Withdrawn)** The method of claim 93, further comprising assessing whether the agent increases a desired biological response that is impaired in subjects having a disorder that is characterized by glucose intolerance, insulin resistance, or decreased mitochondrial function.

115. **(Previously Presented)** The method of claim 93, wherein step (a) is performed in vitro, and the method further comprises administering the agent to a mammalian organism.

116. **(Previously Presented)** The method of claim 115, wherein the mammalian organism is human.

117. **(Previously Presented)** The method of claim 115, wherein the mammalian organism is a test animal that serves as a model for a disorder characterized by glucose intolerance, insulin resistance, or decreased mitochondrial function.
118. **(Previously Presented)** The method of claim 93, wherein the test cell is a mammalian cell.
119. **(Previously Presented)** The method of claim 118, wherein the test cell is a skeletal muscle cell.
120. **(Previously Presented)** The method of claim 118, wherein the test cell is in an organism.
121. **(Previously Presented)** The method of claim 118, wherein the agent to be assessed is a small molecule.
122. **(Previously Presented)** The method of claim 93, wherein the method is performed in parallel on multiple populations of cells and each population is contacted with a different agent to be assessed.
123. **(Previously Presented)** The method of claim 122, wherein the agents are members of a compound library.
124. **(Previously Presented)** The method of claim 109, wherein the agent is useful for treating a human suffering from a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function.
125. **(Previously Presented)** The method of claim 111, wherein the agent is useful for treating a human suffering from a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function.
126. **(Previously Presented)** The method of claim 93, further comprising determining whether the agent also regulates expression of genes that are not OXPHOS-CR genes.

127. **(Previously Presented)** The method of claim 93, wherein step (a) comprises contacting (i) an agent to be assessed for its ability to regulate expression of OXPHOS-CR genes with (ii) a test cell in vitro.